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Myoglobin in third trimester amniotic fluid of human pregnancy — a potential indicator of fetal hypoxia

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1 Introduction

Since radioimmunoassays for specific and sensitive myoglobin measurements are available, they are increasingly applied in the clinical diagnosis of hypoxic, traumatic or metabolic lesions in cardiac and skeletal muscle [1]. Myoglobin assays in plasma are of special use in the diagnosis and prognostic assessment of acute myocardial infarction, crush syndrome and hereditary myopathies, Duchenne muscular dystrophy for example. Strenuous physical exercise and sport activity may increase the serum myoglobin levels [11]. A marked elevation in plasma myoglobin levels was observed after tourniquet ischemia [6].

In healthy subjects, myoglobin is present in the blood at very low levels. Myoglobinemia at elevated levels appears as a result of muscle cell breakdown or membrane leakage. When myoglobin in plasma reaches high concentrations, it is excreted in the urine in considerable amounts.

Myoglobin is an iron-containing, oxygen-binding, purple-colored hemoprotein of monomer structure and a molecular weight of 17.000 daltons (152 amino acids) [7]. Its presence is confined to striated muscle cells. One mole of myoglobin reversibly binds one mole of O_2. The affinity of myoglobin to O_2 is six to seven times as high as that of hemoglobin. Thus, myoglobin releases O_2 only at very low oxygen pressures such as occur in muscle as a consequence of exercise and hypoxia. The biological function of myoglobin is oxygen storage within the muscle cells and its release to the energy-providing mitochondria on demand [2].

Skeletal and cardiac muscle of long-term diving animals, whales and seals for example, are very rich in myoglobin; the oxygen storage property of myoglobin enables them spending longer periods of time underwater. The human fetus is living and growing under low oxygen pressure, and it is not seldom exposed to life-threatening periods of hypoxia and asphyxia, suggesting that myoglobin may be of relevance to the fetus at risk.

In the pertinent literature there were currently no established levels for amniotic fluid myoglobin in late pregnancy, nor any indications as to their clinical significance. Therefore, the major objectives of the present pilot study were the following: to investigate whether and to what extent myoglobin was detectable in human amniotic fluid antepartum and intrapartum, and whether elevated amniotic fluid myoglobin levels were concomitant with certain pathological conditions such as fetal distress provoked by intrauterine hypoxia or intrapartal muscle injury on vaginal delivery.

2 Materials and methods

195 amniotic fluid samples from the third trimester were assayed for their content of myoglobin. 151 of them were obtained by transcervical amniocentesis *intrapartum*. The rest of 44 samples was taken by ultrasound-guided amniocentesis *antepartum*. The antenatal withdrawals of amniotic fluid were generally made within one week prior to delivery. They were chiefly performed to assess fetal lung maturity by means of phospholipid analyses in the liquor.

In order to separate cells, detritus and vernix from amniotic fluid, the samples were centrifuged at 1100 g for 10 minutes. Until processing they were stored in polypropylene tubes at −20 °C.

Myoglobin was determined by radioimmunoassay with reagents supplied by Commissariat à l'énergie atomique, Gif-sur-Yvette, France, and by Sorin Biomedica, Saluggia, Italy. ^{125}I-labeled human myoglobin was used as the tracer, and highly purified human myoglobin was applied for the standards. The myoglobin antiserum from rabbit had full reactivity with human myoglobin and no cross-reactivities with related compounds of human origin, especially with hemoglobin. Even intense hemolytic admixture with the amniotic fluid did not interfere with the assay. The separation of the bound and the free fraction was accomplished with an immuno-precipitating agent containing a second antibody raised in the donkey and directed towards the rabbit antiserum, and polyethylene glycol solution. The RIA-sensitivity was 3 ng myoglobin per ml ($B_0 - 2sB_0$). At concentrations of 15 ng myoglobin per ml, the intra-assay and inter-assay coefficients of variation were 5.1 and 6.5 per cent respectively.

The sample volume per RIA tube was 0.1 ml. The myoglobin assays were performed in triplicate for the standard solutions and in duplicate for the amniotic fluid samples.

3 Results

Depending on the myoglobin levels measured, different amniotic fluid groups could be formed: (A) amniotic fluids containing no myoglobin or traces of it (< 3 ng/ml), (B) amniotic fluid samples with moderately elevated myoglobin levels (3–10 ng/ml) and (C) amniotic fluids with high myoglobin levels (> 10 ng/ml).

The above-defined groups were brought in relation to findings of perinatal fetal monitoring, course and mode of delivery and neonatal outcome.

3.1 Myoglobin in amniotic fluid intrapartum

As can be seen from tables I and II, almost two thirds of the amniotic fluid samples taken intrapartum (n = 98, 64.9% of 151) had myoglobin levels above 3 ng/ml (range 3.7–184 ng/ml). The individual values are represented in figure 1. The rest of 53 samples contained no myoglobin or traces of it which lay below the lower limit of detection of the radioimmunoassay used in this study.

Table I. Intrapartum myoglobin levels in amniotic fluid and selected clinical parameters

	Mb < 3 ng/ml (Group A)	Mb 3–10 ng/ml (Group B)	Mb > 10 ng/ml (Group C)
Amniotic fluid samples assayed	n = 53	n = 54	n = 44
Full-term infants[1]	98.1% (= 52/53)	87.0% (= 47/54)	86.4% (= 38/44)
Premature infants	1.9% (= 1/53) (wk. 36)	13.0% (= 7/54) (wks. 34–36)	13.6% (= 6/44) (wks. 31–36)
Birthweight (means and s.d.) all infants examined	3530 (529) g	3420 (511) g	3260 (697) g
Placental weight (means and s.d.) all cases examined	633 (121) g	666 (160) g	593 (141) g
Small-for-date neonates[2] mean weight	3.8% (= 2/53) 2650 g	7.4% (= 4/54) 2606 g	9.1% (= 4/44) 2053 g
Large-for-date neonates[3] mean weight	20.8% (= 11/53) 4270 g	20.4% (= 11/54) 3988 g	9.1% (= 4/44) 4096 g
Delivery by cesarean section	5.7% (= 3/53)	13.0% (= 7/54)	18.2% (= 8/44)

[1] Full-term infants: delivery at 37 to 42 weeks of gestation
[2] Small-for-date infants: infants with a birthweight below the 10th percentile for gestational age according to NICKL [10]
[3] Large-for-date infants: infants with a birthweight above the 90th percentile for gestational age according to NICKL

Table II. Intrapartum myoglobin levels in amniotic fluid related to findings of fetal and neonatal monitoring

	Mb < 3 ng/ml (Group A)	Mb 3–10 ng/ml (Group B)	Mb > 10 ng/ml (Group C)
Amniotic fluid samples assayed	n = 53	n = 54	n = 44
Pathological CTG[1] antepartum	0% (= 0/26)	0% (= 0/7)	8.0% (= 2/25)
Pathological CTG intrapartum	5.1% (= 2/39)	15.0% (= 3/20)	24.1% (= 7/29)
Meconium-stained amniotic fluid	22.6% (= 11/53)	27.8% (= 15/54)	38.6% (= 17/44)
Metabolic acidosis[2] in the neonate immediately after delivery	7.5% (= 4/53)	11.3% (= 6/53)	23.3% (= 10/43)
Neonatal depression[3] immediately postpartum	3.8% (= 2/53)	0% (= 0/54)	11.4% (= 4/44)
Neonatal depression 5 min postpartum	0% (= 0/53)	0% (= 0/54)	2.3% (1/44)

[1] CTG evaluation according to FIGO Guidelines 1987 [3].
The number of the amniotic fluid samples assayed is not necessarily in accordance to that of monitoring data, since the specified examinations were not performed in each of the examined pregnancies.
[2] pHqu40 < 7.25 in umbilical artery blood; pHqu40 = pH after equilibration with pCO_2 40 mm Hg
[3] Neonatal depression: < 7 points of modified APGAR score [12].

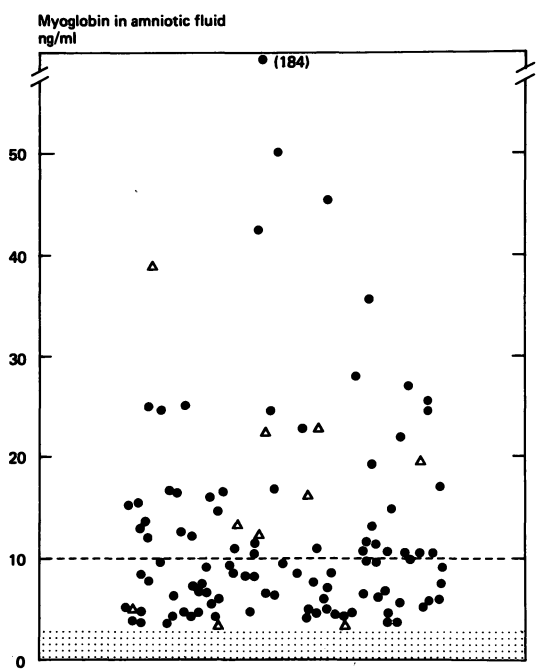

Figure 1. Distribution of the individual myoglobin levels in amniotic fluid above 3 ng/ml. Black dots = myoglobin in amniotic fluid taken intrapartum; open triangles = myoglobin in amniotic fluid drawn antepartum

Table I shows that in Group C (high myoglobin levels) the prevalence of premature and small-for-date infants was larger than in Group A and B. In Group C there were 18.2% of cesarean deliveries due to protracted labor and/or fetal distress, compared to only 5.7% in Group A ($p < 0.05$, $\chi^2 = 5.10$, 1 degree of freedom). The 13% of cesareans in Group B were between the values of Group A and C.

The relative frequency of meconium-stained amniotic fluid samples was significantly higher in Group C than in Group A ($p < 0.05$, $\chi^2 = 4.04$); table II. The prevalence of metabolic acidosis (pHqu40 < 7,25) in the neonate immediately after delivery was three times as high in Group C as in Group A ($p < 0.025$, $\chi^2 = 6.05$). Among the cardiotocograms recorded intrapartum there were considerably more pathological findings in Group C (24.1%) than in Group A (5.1%); $p < 0.01$, $\chi^2 = 7.02$.

Neonatal depression immediately postpartum (Apgar < 7 points) amounted to 11.4% in Group C compared to 3.8% in Group A, a remarkable difference which, however, did not reach the limit of statistical significance of $p < 0.05$. Large-for-date neonates were under-represented in Group C compared with their occurrence in the two other groups.

3.2 Myoglobin in amniotic fluid antepartum

Out of the 44 amniotic fluid samples drawn antepartum, only 10 (= 22.7%) had myoglobin concentrations exceeding 3 ng/ml (range 3.1–39 ng/ml). The individual levels are shown in figure 1 (open triangles).

25 of the antepartal amniotic fluid samples came from pregnancies resulting in preterm delivery, the rest from pregnancies with full-term babies. In Group C the proportion of pregnancies leading to preterm birth was very high (table III).

More than half of the neonates in Group B and C was delivered by cesarean section because of imminent or incipient intrapartum fetal distress. In the pregnancies with myoglobin-positive amniotic fluid samples antepartum, the relative frequency of cesarean deliveries was significantly higher than that in pregnancies with no myoglobin in the liquor amnii antepartum (B+C vs. A, $p < 0.025$, $\chi^2 = 6.57$). In Group C more meconium-stained amniotic fluid samples were to be found than in Group A ($p < 0.05$, $\chi^2 = 4.98$). Similarly, more pathological findings were noticed in

Table III. Antepartum myoglobin levels in amniotic fluid and selected clinical parameters

	Mb < 3 ng/ml (Group A)	Mb 3–10 ng/ml (Group B)	Mb > 10 ng/ml (Group C)
Amniotic fluid samples assayed	n = 34	n = 3	n = 7
Full-term infants	50.0% (= 17/34)	33.3% (= 1/3)	14.3% (= 1/7)
Premature infants	50.0% (= 17/34) wks. 31–36	66.6% (= 2/3) wks. 31–36	85.7% (= 6/7) wks. 30–36
Birthweight (means and s.d.) all infants examined	2942 (638) g	2020 (698) g	2047 (800) g
Placental weight (means and s.d.) all cases examined	587 (117) g	373 (119) g	431 (198) g
Delivery by cesarean section	23.5% (= 8/34)	66.6% (= 2/3)	57.1% (= 4/7)

Table IV. Antepartum myoglobin levels in amniotic fluid related to findings of fetal and neonatal monitoring

	Mb < 3 ng/ml (Group A)	Mb 3–10 ng/ml (Group B)	Mb > 10 ng/ml (Group C)
Amniotic fluid samples assayed	n = 34	n = 3	n = 7
Pathological CTG antepartum	6.7% (= 2/30)	0% (= 0/2)	25.0% (= 2/8)
Meconium-stained amniotic fluid antepartum	2.9% (= 1/34)	0% (= 0/3)	14.3% (= 1/7)
Meconium-stained amniotic fluid intrapartum	11.8% (= 4/34)	0% (= 0/3)	14.3% (=1/7)
Pathological CTG intrapartum	17.2% (= 5/29)	–	33.3% (= 2/6)
Metabolic acidosis in the neonate immediately after delivery	11.8% (= 4/34)	0% (= 0/3)	14.3% (= 1/7)
Neonatal depression immediately postpartum	11.8% (= 4/34)	33.3% (= 1/3)	57.1% (= 4/7)
Neonatal depression 5 min postpartum	2.9% (= 1/34)	0% (= 0/3)	28.6% (= 2/7)

the antepartally recorded cardiotocograms of Group C in comparison with those of Group A ($p < 0.05$, $\chi^2 = 4.62$); table IV.

The occurrence of neonatal depression immediately postpartum was greatly elevated in Group B (33%) and in Group C (57%), related to the approximate 12% in Group A (A vs. C, $p < 0.01$, $\chi^2 = 10.77$). 5 minutes later, the depression rate in Group C was still close to 29%, whereas in Groups A and B it had meanwhile been minimized.

The rate of metabolic acidosis in the neonates immediately postpartum did not differ remarkably in the myoglobin-positive groups from that in the myoglobin-negative one.

4 Discussion

As it is shown by the foregoing results, elevated myoglobin levels in third trimester amniotic fluid are particularly often connected with clinically manifest disorders of pregnancy in the antepartum period or during labor.

In the myoglobin-positive **intrapartum** cases, the statistical prevalence of pathological cardiotocograms during labor, of meconium-stained amniotic fluids, of metabolic acidoses in umbilical artery blood immediately after delivery and – not at least – of an increased rate of emergency cesarean sections give us reason for assuming that episodes of fetal hypoxemia may play a major part in the appearance of myoglobin in amniotic fluid. In our random sample, macrosomia is not associated with raised myoglobin levels in amniotic fluid.

In the pregnancies with positive amniotic fluid myoglobin findings **antepartum**, there is also a statistical prevalence in clinical signs pointing to fetal hypoxic distress such as pathological cardiotocograms antepartum and increased antepartal appearance of meconium in amniotic fluid. The rate of cesarean births for fetal distress is significantly increased in the groups showing elevated amniotic fluid myoglobin levels antepartum compared with the myoglobin-negative group. Neonatal depression immediately postpartum was very frequent among the infants of Group B and C, who were to a larger proportion premature and delivered by cesarean section under general anesthesia.

Recently JENSEN et al [5] investigated the effect of acute asphyxia (4 min arrest of uterine blood flow in the mother animal) on blood flow distribution in central and peripheral organs – including skeletal muscle – of unanesthetized fetal sheep near term. As soon as one minute after onset of asphyxia, they found an extreme drop in muscle perfusion to 2–3% of that in the unasphyxiated control animals. Simultaneously the blood flow to vital organs such as heart, brain stem and adrenals remained nearly unchanged and even increased slowly later on.

The relevant observations strengthened our previous working hypothesis as to the probable origin of myoglobin in amniotic fluid: periods of serious intrauterine hypoxia provoke a hemicirculatory centralization and a profound reduction in blood and oxygen supply to skeletal muscle non-vital to the fetus [13]. This may lead to a membrane leakage in skeletal muscle resulting in myoglobin loss from the myocytes, transitory hypermyoglobinemia and consecutive myoglobin excretion to amniotic fluid.

Since some degree of hypoxemia is almost inevitable in most fetuses during (complicated) vaginal delivery, this may explain the increased rate of elevated myoglobin in amniotic fluid intrapartum (64.9%) in contrast to amniotic fluid antepartum (22.7%).

Serum myoglobin levels were found to be significantly elevated in asphyxiated neonates immediately after delivery compared with newborn control infants [8]. In this context a paper of HAFTEL et al [4] should be mentioned reporting a case of myoglobinuric renal failure in a newborn infant who was severely depressed and had persistent hypoxia and acidosis for several hours after parturition.

Serum myoglobin levels in neonates immediately postpartum do not correlate significantly with those in their mothers and are higher than the maternal ones, suggesting that myoglobin transfer across the placental barrier, which could influence the myoglobin concentrations in amniotic fluid, is extremely low and negligible [15].

In two cases, elevated myoglobin levels in second trimester amniotic fluid from fetuses with Duchenne muscular dystrophy were described [14, 9].

So far, there were no studies in the literature dealing with causal connections between amniotic fluid myoglobin in the perinatal period and hypoxia in the fetus. The present study demonstrates that detection of high myoglobin levels in amniotic fluid during late pregnancy or labor may prove to be an additional new sign of fetal distress.

Summary

195 amniotic fluid samples from the third trimester were examined for their content of myoglobin by means of radio-immunoassay. 151 of the samples were obtained intrapartum, the rest (44) was taken antepartum by transabdominal amniocentesis within one week prior to delivery. Depending on the myoglobin levels measured, different amniotic fluid groups were defined: (A) amniotic fluids containing no myoglobin or traces of it (< 3 ng/ml), (B) amniotic fluids with moderately elevated myoglobin levels (3–10 ng/ml), (C) amniotic fluids with high myoglobin levels (> 10 ng/ml). Myoglobin levels above 3 ng/ml could be measured in 98 of the 151 samples taken intrapartum. In the amniotic fluids drawn antepartum the proportion of "myoglobin-positive" samples (> 3 ng/ml) amounted to only 22.7% (10 out of 44 samples).

In pregnancies with amniotic fluids showing high myoglobin levels intrapartum, the prevalance of meconium staining of the samples, pathological cardiotocograms intrapartum and metabolic acidoses in umbilical artery blood samples was significantly higher than in pregnancies with myoglobin-negative amniotic fluids. The frequency of cesarean sections for fetal distress rose with increasing myoglobin levels in amniotic fluid, being 5.7, 13, and 18.2% in Group A, B and C respectively.

In the pregnancies in which the amniotic fluid samples were taken antepartum, the prevalence of meconium-stained amniotic fluid increased with elevating amniotic fluid myoglobin ($p < 0.05$, Group A vs. Group C). The frequency of cesarean sections for fetal distress and of neonatal depression immediately after delivery was considerably heightened in the cases with myoglobin-positive amniotic fluids antepartum compared to those with myoglobin-negative liquor. The antepartum withdrawals of amniotic fluid were performed predominantly in pregnancies at risk that resulted in preterm delivery. Elevated myoglobin levels in amniotic fluid were mainly associated with an increased prevalence of fetal distress, complicated delivery, and prematurity.

On the assumption that transient seepage of fetal muscle myoglobin into amniotic fluid occurs after periods of fetal hypoxia, the evidence of elevated myoglobin levels in antepartum amniotic fluid appears to be an additional new indicator of hypoxic impairment in the fetus.

Keywords: Amniotic fluid, complicated delivery, fetal distress, hypoxia, myoglobin, neonatal outcome, prematurity.

Zusammenfassung

Myoglobin im Fruchtwasser aus dem dritten Trimenon der menschlichen Schwangerschaft — ein potentielles Hinweiszeichen auf fetale Hypoxie

195 Fruchtwasserproben aus dem dritten Trimenon wurden mittels Radioimmunoassay auf ihren Myoglobingehalt untersucht. 151 Proben wurden intra partum entnommen, die übrigen 44 ante partum in der Woche vor der Entbindung. Abhängig von den gemessenen Myoglobinkonzentrationen, wurden verschiedene Fruchtwassergruppen definiert: (A) Fruchtwässer mit Myoglobinspuren oder ohne Myoglobin (< 3 ng/ml), (B) Fruchtwässer mit mäßig erhöhten Myoglobinkonzentrationen (3–10 ng/ml), (C) Fruchtwässer mit hohen Myoglobinkonzentrationen (> 10 ng/ml). Myoglobinkonzentrationen über 3 ng/ml wurden bei 98 der intra partum entnommenen Proben gemessen, d. s. 64.9%. In der ante partum gewonnenen Fruchtwässern betrug der Anteil der „myoglobin-positiven" Proben nur 22.7% (10 aus 44 Proben).

Bei Schwangerschaften mit Fruchtwässern, die intra partum hohe Myoglobinkonzentrationen aufwiesen, war die Prävalenz von Mekonium im Fruchtwasser, pathologischen Kardiotokogrammen intra partum und metabolischen Azidosen im Nabelarterienblut der soeben Neugeborenen signifikant höher als bei Schwangerschaften mit „myoglobin-negativem" Fruchtwasser. Die Sektiofrequenz wegen fetaler Notsituation stieg mit höheren Myoglobinkonzentrationen im Fruchtwasser an, und zwar von 5.7% über 13% auf 18.2% in den Gruppen A, B bzw. C.

Bei den Schwangerschaften mit Entnahme von Fruchtwasserproben ante partum gab es eine steigende Prävalenz von Mekonium im Fruchtwasser und pathologischen Kardiotokogrammen ante partum, je höher die Myoglobinkonzentrationen in den Fruchtwasserproben waren. Die Häufigkeit von Kaiserschnitten wegen fetaler Notsituation sowie von neonatalen Depressionen sofort post partum war in den Fällen mit myoglobin-positiven Fruchtwässern deutlich erhöht im Vergleich zu den myoglobin-negativen Fällen.

Die antepartualen Fruchtwasserentnahmen wurden vorwiegend bei Risikoschwangerschaften durchgeführt, die mit Frühgeburten endeten.

Erhöhte Myoglobinkonzentrationen im Fruchtwasser gingen hauptsächlich mit einer vermehrten Prävalenz von Symptomen der Fetalgefährdung, komplizierten Entbindung und Frühgeburten einher.

Unter der Annahme, daß vorübergehender Myoglobinaustritt vom fetalen Muskel ins Fruchtwasser vor allem nach Hypoxieperioden auftritt, scheint der Nachweis von erhöhten Myoglobinkonzentrationen im Fruchtwasser ante partum ein zusätzliches, neues Hinweiszeichen auf hypoxische Beeinträchtigung des Feten darzustellen.

Schlüsselwörter: Entbindungskomplikationen, fetale Notsituation, Frühgeburtlichkeit, Hypoxie, Myoglobin im Fruchtwasser, Neugeborenenzustand.

Résumé

Un indicateur potentiel d'hypoxie fœtale: la myoglobine dans le liquide amniotique au cours du troisième trimestre de la grossesse humaine

On a étudié au moyen de dosage radio-immunologique la teneur en myoglobine de 195 échantillons de liquide amniotique au cours du troisième trimestre: 151 échantillons ont été obtenus pendant le travail, le reste (44) a été prélevé par amniocentèse transabdominale au cours de la semaine précédant l'accouchement. On a défini différents groupes de liquides amniotiques en fonction des taux de myoglobine:

a/ — Les liquides n'en contenant pas ou des traces (inférieur à 3 ng/ml)

b/ — Les liquides en contenant des taux moyennement élevés (3—10 ng/ml)

c/ — Les liquides avec taux élevés (supérieur à 10 ng/ml).

On a mesuré des taux de myoglobine supérieurs à 3 ng/ml dans 98 des 151 échantillons prélevés en par partum. Parmi les liquides amniotiques prélevés en pré partum la proportion de liquides «myoglobine positifs» n'est que de 22,7% (10 des 44).

La prévalence de liquide teintés, de cardiotocogrammes pathologiques pendant le travail et d'acidose métabolique au sang artériel ombilical est significativement plus élevée pour les grossesses dont les liquides amniotiques montraient des taux élevés de myoglobine en par partum que pour les grossesses avec des liquides sans myoglobine.

La fréquence des césariennes pour souffrance fœtale s'élève avec l'augmentation du taux de myoglobine du liquide amiotique, elle est respectivement de 5,7, 13, 18,2% dans les groupes a, b et c.

Pour les grossesses dont le liquide amniotique a été prélevé en pré partum, la prévalence des liquides teintés et de cardiotocogrammes pré partum pathologiques s'élève avec l'augmentation de la myoglobine (p inférieur à 0,05, groupe a VS groupe c). La fréquence des césariennes pour souffrance fœtale et des dépressions néonatales immédiatement après la naissance est considérablement plus grande dans les cas où les liquides amniotiques pré partum sont «myoglobine positifs» en comparaison des liquides «myoglobine négatifs». Les prélèvements pré partum des liquides amniotiques ont été réalisés avant tout lors de grossesse à risque entrainant des accouchements prématurés. Des taux élevés de myoglobine s'accompagnant principalement d'une élévation de la prévalence des souffrances fœtales, d'accouchements prématurés et de prématurité.

Dans l'hypoxie où survient un passage transitoire de la myoglobine musculaire fœtale dans le liquide amniotique après des périodes d'anoxie fœtale, l'apparition de taux élevés de myoglobine dans le liquide amniotique en pré partum semble être un nouvel indicateur supplémentaire d'hypoxie fœtale.

Mots-clés: Accouchement compliqué, devenier néonatal, hypoxie, liquide amniotique, myoglobine, prématurité, souffrance fœtale.

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